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COMMENTARY

Rationale and Design of the Chronic GVHD Cohort Study: Improving Outcomes Assessment in Chronic GVHD

The Chronic GVHD Consortium

In 2005, the National Institutes of Health sponsored a Consensus Development Project on Criteria for Clinical Trials in chronic graft-versus-host (cGVHD) to achieve consensus about key elements of cGVHD research, including definitions for diagnosis, severity scoring, and response measures. To test these proposed definitions, a multicenter prospective cohort study of people with cGVHD is ongoing. This study will evaluate the performance of proposed prognostic factors, measures of disease activity, and surrogate endpoints for therapeutic response. Data are collected at 6-month intervals in a heterogeneous population of patients reflecting modern transplant techniques and posttransplantation clinical management (target enrollment 672 with cGVHD from 10 transplantation centers). This report describes the rationale, design, and methods of the cGVHD cohort study, and invites other investigators to collaborate with the Consortium to analyze data or specimens.

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KEY WORDS: Chronic graft-versus-host disease, Allogeneic hematopoietic cell transplantation, Outcomes research, Observational clinical study

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a common immune-mediated disorder following allogeneic hematopoietic cell transplantation (HCT), occurring in 30% to 70% patients [1,2]. Historically, cGVHD was distinguished from acute GVHD (aGVHD) based on its occurrence beyond day 100 after HCT, and severity was classified as limited or extensive based on target organ involvement [3]. Skin, mouth, eye, and liver are historically the most frequently involved organs [4,5]. Chronic GVHD is associated with worse quality of life [6-8], prolonged duration of immunosuppressive therapy [9], and higher nonrelapse mortality (NRM), but also a lower relapse rate [10].

Although cGVHD is associated with high morbidity and mortality following HCT, little substantive progress has been made over the last 3 decades. The National Institutes of Health (NIH) organized a consensus conference in 2005 aimed at consolidating expert opinion to standardize approaches to diagnosis, scoring, histopathology, biomarkers, response assessment, and the conduct of clinical trials in cGVHD [11-16]. It was acknowledged that collection of prospective data was necessary for validation of these recommendations, and future modifications were anticipated as data became available.

The Chronic GVHD Consortium is conducting a multicenter, prospective, longitudinal study designed to validate and refine the recommendations of the NIH Consensus Conference, and to provide improved tools for clinical trials in cGVHD. This article outlines the design and methods of the Chronic GVHD Cohort study, describes the first 546 enrolled patients, and provides information about accessing materials and data from the study.

METHODS

Objectives

The study has 2 major objectives: (1) evaluate whether prognostic measures at onset of cGVHD predict overall and disease-free survival (DFS), NRM, and functional impairment; (2) evaluate proposed measures of cGVHD disease activity for association with (a) *short-term* outcomes, including changes in cGVHD medications, clinician grading of cGVHD severity and change, and patient self-assessment of cGVHD severity and change; and (b) *long-term* outcomes, including overall survival (OS), time to discontinuation of systemic immunosuppressive therapy, and functional impairment.

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Collection of standardized data prospectively from providers and patients will address the limitations of prior studies that relied on medical chart review.

Population

Allogeneic HCT recipients were eligible for inclusion in this study if they were 2 years or older, had a clinical diagnosis of cGVHD (overlap syndrome with concurrent manifestations of both cGVHD and aGVHD was allowed), and were receiving systemic treatment for cGVHD, defined as any medication or intervention delivered systemically, including extracorporeal photopheresis. Any graft source, donor type, and GVHD prophylaxis was allowed. Prevalent cases (defined as enrollment 3 or more months after cGVHD diagnosis) were within 3 years of stem cell infusion. Incident cases (enrollment less than 3 months after diagnosis) had no limitation on time from transplantation. Patients were excluded if they were unable to comply with study procedures, had evidence of primary disease relapse, or had an anticipated survival less than 6 months because of comorbid disease. At Fred Hutchinson Cancer Research Center, a limited number of patients with late-onset, persistent, or recurrent aGVHD were also enrolled (n = 9) [12] as were control patients without cGVHD as a comparison group (n = 42). In order to be considered a control, participants had no diagnostic criteria for cGVHD and did not develop any in the 3 months after enrollment. Controls may still be receiving systemic immune suppressive medications for prophylaxis or treatment of aGVHD. The protocol is institutional review board (IRB)-approved at all participating sites, and all participants provided written informed consent. This study was registered at www.clinicaltrials.gov as #NCT00637689. Participating transplantation centers and investigators are listed in the Appendix (Figure 1).

Study Design

This is a prospective, longitudinal observational study. No therapeutic interventions are mandated by the protocol. Target enrollment is 672 patients at 10 transplantation centers. Unfortunately, the Consortium is unable to accept new sites.

At the time of enrollment and every 6 months, providers and patients provide standardized information about organ involvement and symptoms. Incident cases have an additional assessment at 3 months after enrollment. Chart review is used to document objective medical data (including ancillary testing and laboratory results), medical complications, and medication profiles (Table 1). Serial assessments are performed until recurrent malignancy develops requiring immunotherapy (rapid tapering of immunosuppression or donor lymphocyte infusions) or antineoplastic therapy, cGVHD resolves for 1 year, or the end of the study, whichever occurs first. Patients who are not seen at the transplant center for their semiannual assessments are sent the patient-reported surveys by mail and outside medical records are reviewed for clinical information, but no provider assessment form is collected.

Data Collection

Data are entered into an electronic database maintained at the Coordinating Center at Fred Hutchinson Cancer Research Center using only a study identification number (ID). Data are cleaned every 3 months using customized programs for range and logic checking, and by random audits comparing entry to source documents.

Provider assessment form

Providers report data as recommended by the NIH Consensus Conference for cGVHD individual organ involvement, as well as the presence of specific findings such as bronchiolitis obliterans syndrome. Providers report a global rating of current disease severity (mild, moderate, or severe; and 0-10) and perceptions of change (a 1-8 scale from "completely resolved" to "very much worse"). Additional items that are collected even though they were not recommended by the NIH Consensus Conference include reasons for medication changes, justification of the global rating score, an overall assessment of response (complete response, partial response, stable, or progression), perceptions of disease activity, and identification of a sentinel organ to judge success of therapy. Providers also complete endpoint measures used in previous cGVHD clinical studies such as the Johns Hopkins items for skin, fascia, and mouth involvement [17] and the Vienna Skin Score [18,19]. The battery of provider forms takes approximately 10 minutes to complete once the physical exam and interview are completed. Online

Figure 1. Location of enrolling centers in the Chronic GVHD Consortium.

Table 1. Data Collection for the Cohort Study

Data Element	Data Source	Description
Provider assessment form	Clinical providers	NIH organ scores, Johns Hopkins organ scores, Vienna skin score, NIH response measures, range of motion, overall chronic GVHD severity, sentinel organ, reason for adjusting treatment, rare clinical manifestations, perceptions of change
Patient assessment form	Patients	FACT-BMT, SF-36, Lee symptom scale, HAP, ODSI, ASK, overall chronic GVHD severity, perceptions of change
Functional assessments	Patients	FEV_1 via portable spirometer, grip strength, 2-minute walk test, Schirmer's test
Chart review	Institutional database or medical records	Patient, donor, and transplant characteristics, immuosuppressive medications, comorbidity, biopsy dates, number of hospital days, relapse, death, resolution of chronic GVHD
Biological samples	Limited institutions	Serum, plasma, peripheral blood mononuclear cells, urine

GVHD indicates graft-versus-host disease; FACT-BMT, functional assessment of cancer therapy-bone marrow transplant version 4.0; SF-36, short form-36 v2.0; HAP, human activities profile; ODSI, ocular disease surface index; ASK, Activities Scale for Kids; FEV_1, forced expiratory volume, first second.

training in completion of the provider assessment forms is available on the Web [20,21].

Functional assessments

Clinical or study staff perform and record functional status measures. Grip strength is measured 3 times from the dominant hand using a portable electronic dynamometer. Three measures of forced expiratory volume, first second (FEV_1) are recorded using a portable spirometer. The 2-minute walk test requires the patient to walk a 50-foot course (25 feet each direction), and the total distance covered after 2 minutes is recorded. Finally, bilateral Schirmer's test is performed without anesthesia. Of these tests, the grip strength, walk test, and Schirmer's test are recommended by the NIH Consensus Conference. The functional testing takes approximately 20 minutes to collect.

Patient assessment form

Patients report their symptoms, global severity scores, perceptions of change, quality of life, and functional status. The Functional Assessment of Cancer Therapy-Bone Marrow Transplant subscale (FACT-BMT), SF-36, Chronic GVHD Symptom Scale, Human Activities Profile, and Activities Scale for Kids (ASK) (pediatrics only) are collected, as recommended by the consensus conference [14]. In addition, patients complete the Ocular Surface Disease Index (OSDI). Scoring follows the recommendations of the developers but generally follows the tenet that a subscale or scale can be scored if more than 50% of the data are present. The battery of patient forms takes approximately 20 to 30 minutes to complete.

The FACT-BMT version 4 is a 49-item self-report questionnaire, which includes a 12-item Bone Marrow Transplant subscale. Patients respond based on their experience over the preceding 7 days. The instrument measures the effect of cancer therapy on multiple quality-of-life (QOL) domains including physical, functional, social/family, and emotional well-being, and bone marrow transplantation (BMT) specific concerns. Individual domain scores are summarized to give a total FACT-BMT score, with higher scores indicating greater quality of life. Abbreviated scores, which can be derived from these data, include a FACT-G summary measure that excludes the BMT-specific subscale, and the FACT-TOI (trial outcome index) score, which consists of the sum of physical and functional well-being and the BMT subscale. The FACT-BMT has been extensively used in investigation of QOL after HCT [22].

The Medical Outcomes Study Short Form version 2.0 (SF-36) is a 36-item self-report questionnaire that assesses general health and functioning. The instrument examines 8 domains of QOL: physical functioning, role functioning-physical, bodily pain, general health, vitality, social functioning, role functioning-emotional, and mental health. Scores range from 0 to 100, with higher scores indicating better functioning. Two summary scales from the SF-36 include the physical component score (PCS) and the mental component score (MCS), which are normalized to the general population with a mean of 50 and standard deviation of 10. The SF-36 has been extensively utilized in diverse biomedical research [23,24].

The Chronic GVHD Symptom Scale is a 30-item, 7-subscale symptom scale developed to capture the symptom burden of patients with cGVHD. The instrument evaluates adverse effects of cGVHD on skin, vitality, lung, nutritional status, psychological functioning, eye, and mouth by asking patients to report the degree of bother they experienced in the past month from their cGVHD symptoms. Scores range from 0 to 100 with higher scores indicating greater symptom burden [25].

The Human Activity Profile (HAP) is a 94-item self-reported assessment of energy expenditure and physical fitness. The HAP was first developed in a population with pulmonary disease [26], and has since been utilized in multiple other chronic health conditions. The HAP has been validated in an HCT population [27]. Two scores are calculated: a maximum activity score (MAS) and an average activity score (AAS). An HCT-specific modified score has been proposed [27].

The Ocular Surface Disease Index (OSDI) is a 12-item validated scale that captures dry eye symptoms [28].

The ASK is a 38-item pediatric measure of physical disability intended for children from 5 to 15 years of age. Questions may be read to nonreaders. There are 9 subdomains: personal care, dressing, eating and drinking, locomotion, stairs, play, transfers, standing skills, and miscellaneous items [29,30].

Medical records abstraction

Information on patient, donor, and transplantation characteristics, cGVHD presentation, and current status is collected from institutional databases or chart review. Immunosuppressive medications at the time of the visit and any given between visits are captured. Comorbidities are recorded at the onset of cGVHD, at the time of enrollment, and when a patient goes off study using items from the Sorror comorbidity index [31] and the functional comorbidity index [32].

Biological samples

At selected institutions, biological samples are also banked in a repository for future studies. For example, at the Fred Hutchinson Cancer Research Center, plasma, serum, peripheral blood mononuclear cells, and urine samples are stored and available by request. Investigators may also access skin biopsy specimens previously collected for clinical purposes. Stanford, University of Minnesota, Dana-Farber Cancer Institute, and Vanderbilt University have repositories; interested investigators should contact individual site Principal Investigators to arrange collaborations.

Biostatistical Considerations

This is a longitudinal observational study with 1 baseline and a variable number of follow-up assessments for each participant. Information from this study will be used to learn how we can most effectively and efficiently assess and document clinical benefit in trials testing new treatment interventions in patients with cGVHD. These determinations will be made based on the following considerations: the extent to which each scale provides reliable and unique information about meaningful outcomes; respondent burden (either provider or patient); and costs and resource utilization required to collect the item.

Missing data are inevitable in any clinical study. Each analysis of study data will describe missing data, examine mechanisms of "missingness," and attempt to account for them. These methods include a comparison of those with and without missing data, documentation of sources of missing data, and evaluations of the pattern of missingness. Centralized multiple imputation of selected variables could be performed in the future [33,34].

Collaboration with Other Investigators

The consortium collaborates with other investigators who wish to access curated data and research samples derived from this study. Before data or samples can be provided, a concept sheet must be discussed by Consortium members and approved by the Consortium Principal Investigator. All ancillary studies require IRB approval or waiver at both the center(s) providing data/samples and the receiving institution(s), as well as a materials transfer agreement or data use agreement if a subcontract is not in place. Approval of the collaboration by the National Cancer Institute may also be required. Data are deidentified, with clinical information and samples designated only by a study ID.

Baseline Characteristics of Cohort

As of March 2011, a total of 546 subjects have been enrolled in this prospective cohort study from 9 transplantation centers. Patient sociodemographics, cGVHD case type, and transplantation variables are summarized in Table 2.

SUMMARY AND CONCLUSIONS

The Chronic GVHD Cohort Study aims to improve outcome assessment in cGVHD. This study will evaluate the natural history of cGVHD under modern treatment regimens, and will evaluate prognostic factors, potential measures of disease activity, and surrogate endpoints for therapeutic response.

The study has a number of strengths including its size, prospective and standardized data collection, and the availability of biologic samples from approximately one-half of participants. Enrollment at many geographically disparate transplantation centers ensures that different management styles and transplantation-related factors are well represented. The study also has a number of weaknesses including that treatment is not standardized and provider-reported data are only as good as the training and experience of the clinician. This study is conducted in the midst of clinical practice, so that patients do not always return when

Table 2. Enrollment Sociodemographic, Chronic GVHD, and Transplantation Characteristics (N = 546)

Characteristic	Chronic GVHD (n = 495) n (%)	Controls, No Chronic GVHD (n = 42)* n (%)	Persistent, Recurrent, or Late Acute GVHD (n = 9) n (%)
Case type			
Incident	283 (57%)	—	—
Prevalent	212 (43%)	—	—
Adult (18+)	481 (97%)	42 (100%)	9 (100%)
Patient age at registration (years)			
Median (range)	51 (2-79)	51 (22-72)	51 (28-61)
Male patients	288 (58%)	19 (45%)	9 (100%)
Hispanic patients	24 (5%)	3 (7%)	0 (0%)
Diagnosis at transplant			
AML	151 (33%)	10 (27%)	2 (22%)
ALL	57 (13%)	5 (13%)	1 (11%)
CML	25 (6%)	1 (3%)	0 (0%)
CLL	34 (7%)	1 (3%)	1 (11%)
MDS	69 (15%)	7 (19%)	3 (33%)
NHL	66 (14%)	5 (13%)	0 (0%)
HD	16 (3%)	2 (6%)	0 (0%)
MM	21 (5%)	5 (13%)	2 (22%)
AA	5 (1%)	0 (0%)	0 (0%)
Other	15 (3%)	1 (3%)	0 (0%)
Disease status			
Early	149 (33%)	12 (32%)	3 (33%)
Intermediate	196 (43%)	12 (32%)	5 (56%)
Advanced	110 (24%)	13 (36%)	1 (11%)
Graft source			
Peripheral blood	405 (88%)	29 (78%)	5 (56%)
Bone marrow	34 (7%)	7 (19%)	1 (11%)
Cord blood	22 (5%)	1 (3%)	3 (33%)
Transplant type			
Myeloablative	261 (57%)	20 (54%)	3 (38%)
Not myeloablative	193 (43%)	17 (46%)	5 (62%)
Patient CMV positive	261 (57%)	15 (41%)	5 (56%)
Donor CMV positive	180 (40%)	15 (41%)	2 (22%)
Donor type			
HLA matched relative	199 (44%)	19 (51%)	3 (33%)
HLA mismatched relative	10 (2%)	5 (14%)	0 (0%)
Unrelated donor	249 (54%)	13 (35%)	6 (67%)
Site			
Fred Hutchinson Cancer Research Center	229 (46%)	42 (100%)	4 (44%)
University of Minnesota	56 (11%)	0 (0%)	5 (56%)
Dana-Faber Cancer institute	58 (12%)	0 (0%)	0 (0%)
Stanford University Medical Center	68 (13%)	0 (0%)	0 (0%)
Northwestern Children's Hospital	13 (3%)	0 (0%)	0 (0%)
Vanderbilt University Medical Center	39 (8%)	0 (0%)	0 (0%)
Medical College of Wisconsin	16 (3%)	0 (0%)	0 (0%)
Washington University	3 (1%)	0 (0%)	0 (0%)
Moffitt Cancer Center	13 (3%)	0 (0%)	0 (0%)
Patient race			
White	442 (89%)	40 (96%)	7 (78%)
Black	13 (2%)	1 (2%)	0 (0%)
Asian	26 (5%)	0 (0%)	1 (11%)
American Indian/Alaskan Native	1 (1%)	1 (2%)	0 (0%)
Native Hawaiian/Pacific Islander	2 (1%)	0 (0%)	0 (0%)
Multi	6 (1%)	0 (0%)	0 (0%)
Unknown	5 (1%)	0 (0%)	1 (11%)
Donor gender			
Female into male	130 (29%)	5 (13%)	1 (11%)
Mixed (cord blood)	9 (2%)	1 (3%)	0 (0%)
Other combinations	317 (69%)	31 (84%)	8 (89%)
Marital status			
Married/living with partner	314 (77%)	20 (62%)	5 (72%)
Single, never married	33 (8%)	5 (16%)	1 (14%)
Divorced, separated	45 (11%)	5 (16%)	1 (14%)
Widowed	11 (3%)	2 (6%)	0 (0%)
Other	4 (1%)	0 (0%)	0 (0%)
Highest education			
Grade school	7 (2%)	0 (0%)	0 (0%)
Some high school	13 (3%)	0 (0%)	0 (0%)
High school graduate	66 (16%)	2 (6%)	1 (14%)
Some college	121 (29%)	5 (16%)	4 (58%)

(*Continued*)

Table 2. (*Continued*)

Characteristic	Chronic GVHD (n = 495) n (%)	Controls, No Chronic GVHD (n = 42)* n (%)	Persistent, Recurrent, or Late Acute GVHD (n = 9) n (%)
College graduate	113 (27%)	15 (49%)	1 (14%)
Post-graduate degree	96 (23%)	9 (29%)	1 (14%)
Annual family income			
Under $15,000	16 (4%)	2 (7%)	0 (0%)
$15,000-$24,999	27 (7%)	1 (4%)	1 (14%)
$25,000-$49,999	60 (16%)	7 (24%)	1 (14%)
$50,000-$74,999	79 (21%)	5 (17%)	4 (58%)
$75,000-$99,999	62 (16%)	5 (17%)	1 (14%)
$100,000 or above	137 (36%)	9 (31%)	0 (0%)

AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; HD, Hodgkin's disease; MM, multiple myeloma; AA, aplastic anemia; CMV, cytomegalovirus; HLA, human leukocyte antigen.
*Eight patients are awaiting confirmation as controls.

desirable and clinician time and resources limit extensive evaluations.

Investigators interested in the clinical data, research forms, database structure, or research samples available from this cohort study should contact the Consortium for procedures on how to apply for access. We welcome collaboration with other investigators involved in cGVHD research.

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APPENDIX: PARTICIPANTS IN THE CHRONIC GVHD CONSORTIUM

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